CLAIMS

We claim:

1. A targeting construct comprising:

(a) a first polynucleotide sequence homologous to a target gene, wherein the target gene is a cGMP phosphodiesterase gene;

(c) a second polynucleotide sequence homologous to the target gene; and

(d) a selectable marker.

2. The targeting construct of claim 1, wherein the targeting construct further comprises a screening marker.

3. A method of producing a targeting construct, the method comprising:

(a) obtaining a first polynucleotide sequence homologous to a cGMP phosphodiesterase gene;

(b) obtaining a second polynucleotide sequence homologous to a cGMP phosphodiesterase gene;

(c) providing a vector comprising a selectable marker; and

(d) inserting the first and second sequences into the vector, to produce the targeting construct.

4. A method of producing a targeting construct, the method comprising:

(a) providing a polynucleotide sequence homologous to a cGMP phosphodiesterase;

(b) generating two different fragments of the polynucleotide sequence;

(c) providing a vector having a gene encoding a selectable marker; and

(d) inserting the two different fragments into the vector to form the targeting construct.

5. A cell comprising a disruption in a cGMP phosphodiesterase gene.

6. The cell of claim 5, wherein the cell is a murine cell.

7. The cell of claim 6, wherein the murine cell is an embryonic stem cell.

8. A non-human transgenic animal comprising a disruption in a cGMP phosphodiesterase.

9. A cell derived from the non-human transgenic animal of claim 8.

10. A method of producing a transgenic mouse comprising a disruption in a cGMP phosphodiesterase gene, the method comprising:

(a) introducing the targeting construct of claim 1 into a cell;

(b) introducing the cell into a blastocyst;

(c) implanting the resulting blastocyst into a pseudopregnant mouse, wherein said pseudopregnant mouse gives birth to a chimeric mouse; and

(d) breeding the chimeric mouse to produce the transgenic mouse.

11. A method of identifying an agent that modulates the expression of a cGMP phosphodiesterase, the method comprising:

(a) providing a non-human transgenic animal comprising a disruption in a cGMP phosphodiesterase gene;

(b) administering an agent to the non-human transgenic animal; and

(c) determining whether the expression of cGMP phosphodiesterase in the non-human transgenic animal is modulated.

12. A method of identifying an agent that modulates the function of a cGMP phosphodiesterase, the method comprising:

(a) providing a non-human transgenic animal comprising a disruption in a cGMP phosphodiesterase gene;

(b) administering an agent to the non-human transgenic animal; and

(c) determining whether the function of the disrupted cGMP phosphodiesterase gene in the non-human transgenic animal is modulated.

13. A method of identifying an agent that modulates the expression of cGMP phosphodiesterase, the method comprising:

(a) providing a cell comprising a disruption in a cGMP phosphodiesterase gene;

(b) contacting the cell with an agent; and

(c) determining whether expression of the cGMP phosphodiesterase is modulated.

14. A method of identifying an agent that modulates the function of a cGMP phosphodiesterase gene, the method comprising:

(a) providing a cell comprising a disruption in a cGMP phosphodiesterase gene;

(b) contacting the cell with an agent; and

(c) determining whether the function of the cGMP phosphodiesterase gene is modulated.

15. The method of claim 13 or claim 14, wherein the cell is derived from the non-human transgenic animal of claim 8.

16. An agent identified by the method of claim 11, claim 12, claim 13, or claim 14.

17. A transgenic mouse comprising a disruption in an cGMP phosphodiesterase gene, wherein the transgenic mouse exhibits an eye abnormality.

18. The transgenic mouse of claim 17, wherein the eye abnormality is a retinal abnormality.

19. The transgenic mouse of claim 18, wherein the retinal abnormality is characterized by retinal degeneration or retinal dysplasia.

20. The transgenic mouse of claim 19, wherein the transgenic mouse exhibits an absence of photoreceptor layers.

21. The transgenic mouse of claim 17, wherein the eye abnormality is consistent with vision problems or blindness.

22. The transgenic mouse of claim 19, wherein the retinal abnormality is consistent with retinitis pigmentosa.

23. The transgenic mouse of claim 17, wherein the eye abnormality comprises at least one of the following: thinning or vacuolation of the inner nuclear layer of the eye; thinning of the inner plexiform layer of the eye; loss of ganglion cell nuclei; gliosis of the nerve fiber layer; or attenuation of retinal vasculature.

24. The transgenic mouse of claim 17, wherein the transgenic mouse is heterozygous for a disruption in an cGMP phosphodiesterase gene.

25. The transgenic mouse of claim 17, wherein the transgenic mouse is homozygous for a disruption in an cGMP phosphodiesterase gene.

26. A method of producing a transgenic mouse comprising a disruption in an cGMP phosphodiesterase gene, wherein the transgenic mouse exhibits an eye abnormality, the method comprising:

(a) introducing an cGMP phosphodiesterase gene targeting construct into a cell;

(b) introducing the cell into a blastocyst;

(c) implanting the resulting blastocyst into a pseudopregnant mouse, wherein said pseudopregnant mouse gives birth to a chimeric mouse; and

(d) breeding the chimeric mouse to produce the transgenic mouse comprising a disruption in an cGMP phosphodiesterase gene.

27. A cell derived from the transgenic mouse of claim 17 or claim 26, wherein the cell comprises a disruption in an cGMP phosphodiesterase gene.

28. A method of identifying an agent that ameliorates an eye abnormality, the method comprising:

(a) administering an agent to a transgenic mouse comprising a disruption in an cGMP phosphodiesterase gene; and

(b) determining whether the agent ameliorates the eye abnormality of the transgenic mouse.

29. The method of claim 28, wherein the eye abnormality is a retinal abnormality.

30. The method of claim 29, wherein the retinal abnormality is characterized by retinal degeneration or retinal dysplasia.

31. The method of claim 28, wherein the transgenic mouse exhibits an absence of photoreceptor layers.

32. The method of claim 28, wherein the eye abnormality comprises at least one of the following: thinning or vacuolation of the inner nuclear layer of the eye; thinning of the inner plexiform layer of the eye; loss of ganglion cell nuclei in the eye; gliosis of the nerve fiber layer of the eye; or attenuation of retinal vasculature in the eye.

33. A method of identifying an agent which modulates cGMP phosphodiesterase expression, the method comprising:

(a) administering an agent to the transgenic mouse comprising a disruption in an cGMP phosphodiesterase gene; and

(b) determining whether the agent modulates cGMP phosphodiesterase expression in the transgenic mouse, wherein the agent modulates a phenotype associated with a disruption in an cGMP phosphodiesterase gene.

34. The method of claim 33, wherein the phenotype comprises an eye abnormality.

35. A method of identifying an agent which modulates a phenotype associated with a disruption in an cGMP phosphodiesterase gene, the method comprising:

(a) administering an agent to a transgenic mouse comprising a disruption in an cGMP phosphodiesterase gene; and

(b) determining whether the agent modulates the phenotype.

36. The method of claim 35, wherein the phenotype comprises an eye abnormality.

37. A method of identifying an agent which modulates cGMP phosphodiesterase expression, the method comprising:

(a) providing a cell comprising a disruption in cGMP phosphodiesterase gene;

(b) contacting the cell with an agent; and

(c) determining whether the agent modulates cGMP phosphodiesterase expression, wherein the agent modulates a phenotype associated with a disruption in an cGMP phosphodiesterase gene.

38. The method of claim 37, wherein the phenotype comprises an eye abnormality.

39. A method of identifying an agent which modulates cGMP phosphodiesterase gene function, the method comprising:

(a) providing a cell comprising a disruption in an cGMP phosphodiesterase gene;

(b) contacting the cell with an agent; and

(c) determining whether the agent modulates cGMP phosphodiesterase gene function, wherein the agent modulates a phenotype associated with a disruption in an cGMP phosphodiesterase gene.

40. The method of claim 39, wherein the phenotype comprises an eye abnormality.

41. An agent identified by the method of claim 28, claim 33, claim 35, claim 37 or claim 39.

42. A transgenic mouse comprising a disruption in an cGMP phosphodiesterase gene, wherein the transgenic mouse exhibits hyperactive behavior.

43. The transgenic mouse of claim 42, wherein the transgenic mouse is heterozygous for a disruption in an cGMP phosphodiesterase gene.

44. The transgenic mouse of claim 43, wherein the transgenic mouse is homozygous for a disruption in an cGMP phosphodiesterase gene.

45. A method of identifying an agent that ameliorates hyperactive behavior, the method comprising:

(a) administering an agent to a transgenic mouse comprising a disruption in an cGMP phosphodiesterase gene; and

(b) determining whether the agent ameliorates hyperactive behavior of the transgenic mouse.

46. A method of identifying an agent which modulates an cGMP phosphodiesterase expression, the method comprising:

(a) administering an agent to the transgenic mouse comprising a disruption in an cGMP phosphodiesterase gene; and

(b) determining whether the agent modulates cGMP phosphodiesterase expression in the transgenic mouse, wherein the agent has an effect on hyperactive behavior of the transgenic mouse.

47. A method of identifying an agent which modulates a phenotype associated with a disruption in a cGMP phosphodiesterase gene, the method comprising:

(a) administering an agent to a transgenic mouse comprising a disruption in a cGMP phosphodiesterase gene; and

(b) determining whether the agent modulates hyperactive behavior of the transgenic mouse.

48. An agent identified by the method of claim 45, claim 46 or claim 47.